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POTASSIUM DEFICIENCY IN RATS: EFFECTS ON RATES OF DEHYDRATION AND ELECTROLYTE HOMEOSTASIS*

R. P. FRANCESCONI,† N. M. LEVA, C. R. JOHNSON and R. W. HUBBARD

U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760-5007, U.S.A.

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Abstract—1. Three groups of rats were fed a nutritionally complete (C), potassium-deficient (−K), or potassium-supplemented (+K) diet for 28 days followed by passive exposure to a moderate heat stress (T_{amb} = 31.5°C) until a hypohydration level of 8–9% of initial body weight was achieved.

2. Significant ($P < 0.05$) hypokalemia was achieved in the −K group and, while final T_{re} was also increased ($P < 0.05$ vs C) in this group, time to achieve hypohydration and water loss during heat stress were unaffected.

3. Potassium (K^+) levels were decreased and sodium (Na^+) concentrations were increased in selected striated muscles of both the +K and −K groups (vs C), but electrolytes in critical tissues (heart, brain, kidney, liver) were unaffected by dietary intake.

4. The moderate hyperthermia achieved during the dehydration interval elicited minor effects on several indices of heat stress/injury.

5. The results suggest that the combination of consumption of a K deficient diet for 28 days and exposure to moderate heat stress did not significantly affect dehydration rates or total water loss, but a slightly elevated final T_{re} was observed in the −K group.

Key Word Index: Hypohydration; tissue electrolytes; potassium deficiency

INTRODUCTION

The early investigations of Knochel and his associates (Knochel and Vertel, 1967; Knochel *et al.*, 1972; Knochel, 1974) identified circulating hypokalemia as a clinical index of predisposition to heat illness. Later, Hubbard *et al.* (1981) demonstrated that prolonged consumption of a potassium deficient (−K) diet led to a significant reduction in treadmill endurance in a rat model of human heatstroke/heat injury (Hubbard *et al.*, 1976, 1978); they attributed the decremented performance to an increased heating rate in the K deficient rats.

We also used a −K diet to investigate the effects of hypokalemia on thermoregulation in rats passively and acutely exposed to extreme environmental heat (T_{amb} = 41–42°C) (Francesconi *et al.*, 1991). In these experiments we showed that when rats were passively exposed to extreme heat, K deficient rats manifested a thermal tolerance (time to T_{re} = 42.6°C) which was approx. 50% (86 min) of that of rats consuming a standard commercially-available diet (178 min). We theorized that factors other than evaporative heat dissipation, probably an increased rate of heat production, contributed to the rapidly elevated T_{re} in the K deficient animals. We based this tentative conclusion on the observation that there were no significant differences in the rate of evaporative water loss during the heat stress interval; however, it should be noted that the ambient temperature selected (41–42°C) represents such a significant physiological challenge for rats that lethality ordinarily ensues within several hours if exposure continues.

Thus, we became interested in determining the effects of hypokalemia on thermoregulation and electrolyte homeostasis when the ambient temperature elicited significant hypohydration with only moderate hyperthermia. In the current experiments, then, we selected ambient conditions that provided a targeted hypohydration (weight loss) level of 8-9% of initial body weight with non-injurious and steady-state final T_{re}. We theorized that the ambient

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†To whom correspondence should be addressed.

temperature selected should provide a period of dehydration of at least 12 h for adequate equilibration of body fluid compartments during hypohydration (Durkot *et al.*, 1986). This design also provided the opportunity to assess the effects of chronic K depletion and hypohydration on electrolyte distribution and several circulating indices of heat illness.

MATERIALS AND METHOD

Adult, male rats (Sprague–Dawley, CD-1, 375–450 g at experiment) were acquired from the Charles River Breeding Laboratories (Wilmington, MA) and maintained in our animal holding facility for at least 1 week prior to use (T_{amb} = 22–24 C, lights on 0600–1800 h). During the entire holding and experimental intervals animals were housed singly in wire-bottomed cages, and food and water were available *ad libitum* except for the removal of water during the dehydration interval. Animals were assigned to one of 3 dietary groups (N = 11–13/group).

Control (C) animals were maintained on a standard, commercially available, and complete rodent diet (Agway Corp., RMH-3000) delivering fiber (5%), fat (5%), protein (22%), ash (6%), and nitrogen free extract (starch, 52%) until the desired weight range was achieved. A second group (+K) was placed on a specially prepared K-supplemented diet which was otherwise identical to the diet consumed by a third group of animals (−K) whose diet was K deficient. Both the −K diet (US Biochemical, Cleveland, OH, Cat. No. 880920AII) and the +K diet (US Biochemical, Cat. No. 881118AII) delivered approx. 28.7% protein, 47.8% sucrose, 3.3% fat, and 13.6% corn starch. The K content of the C diet was 0.95% while that of the +K diet was approx. 0.36%. Experimental rats remained on the +K or −K diet for 28 days.

Two days prior to an experimental trial a catheter was aseptically implanted into the external jugular vein of each rat while under sodium pentobarbital anesthesia. At approx. 1600 h on the 28th day of either experimental diet or approx. 21 days on the C diet, a small blood sample (pre, 0.8 ml) was removed and T_{re} (6 cm insertion) was recorded. Subsequently, animals were placed without drinking water into a large stainless steel chamber [2.7 m(l) × 1.6 m(w) × 2.0 m(h)] maintained at 31.5 ± 0.5 C. During the overnight dehydration the animals ordinarily lost 6–6.5% of their initial body weight (corrected for fecal pellet production); following the first reading (0600 h) of the subsequent morning, weights and temperatures were monitored at 30 min intervals so that the targeted level of hypohydration (8–9% of initial body weight) was accurately achieved. Upon reaching the predetermined body weight, a final T_{re} was recorded, and the rats were then quickly removed to room temperature, a second blood sample was withdrawn (post), and the animals were deeply anethestized for the extraction of muscles (gastrocnemius, soleus, plantaris, diaphragm) and critical organs (kidney, liver, heart, brain).

Fresh blood plasma (10,000 *g*, 4 C) was immediately analyzed for total protein, (refractometry) and an aliquot was stored at 4 C for same day analysis of osmolality (μOsmette, Natick, MA). The remainder of the plasma was frozen (−20 C) and stored for subsequent analysis of several circulating indices of heat injury (Kim *et al.*, 1980; Hart *et al.*, 1982; Costrini *et al.*, 1979). Plasma sodium (Na^+) and K^+ levels were analyzed using standard flame photometry (FLM3, Radiometer, Copenhagen) while Na^+ and K^+ concentrations in tissue were quantitated according to methods described by Moore (1966). Lactic acid dehydrogenase (LDH), creatine phosphokinase (CPK), glucose, urea nitrogen (UN), and creatinine were quantitated using an automated clinical spectrophotometer (Ciba-Corning 550 Express) and commercially available (Ciba-Corning) test kits.

Repeated (multiple factor) and non-repeated (single factor) analyses of variance (BMDP Statistical Software, Los Angeles, CA) were utilized for statistical analysis. Tukey's critical difference test was applied *post hoc* to identify significant differences between respective means. The null hypothesis was rejected at $P < 0.05$.

RESULTS

Table 1 demonstrates that the targeted level of hypohydration (i.e. 8–9%) was achieved in all 3 groups. While the % hypohydration recorded in the C group was statistically ($P < 0.01$) greater than either the +K or −K groups, this was evidently of minor physiological consequence since the more important variables (i.e. time required to achieve hypohydration, total weight loss, and weight loss/min during dehydration) manifested no significant intergroup differences. It is noteworthy that while initial rectal temperatures were not statistically different among groups, the final T_{re} of the −K group was significantly ($P < 0.01$) increased when compared with that of the C group only, with the +K group falling intermediate between the C and −K groups.

Predehydration levels of circulating Na^+ (Table 2) were significantly elevated in both the −K ($P < 0.05$) and +K ($P < 0.01$) groups when compared with C, but, following dehydration, these differences were apparently neutralized. While a significant ($P < 0.01$) hypokalemia was achieved in the −K group, the +K

Table 1. Effects of K deficiency on physiological responses to dehydration by 8 9% of initial body weight

Variable	Control (C)	Potassium replenished (+K)	Potassium depleted (−K)
Hypohydration (% body weight)	8.7 ± 0.1	8.2 ± 0.1*	8.2 ± 0.1*
Time to achieve hypohydration (min)	1087 ± 25	1077 ± 42	1045 ± 28
Total weight loss during dehydration (g)	34.2 ± 0.7	35.6 ± 0.9	33.7 ± 0.5
Weight loss/min during dehydration (mg)	31.7 ± 1.0	33.6 ± 2.0	32.5 ± 1.0
Initial T_{re} (C)	38.0 ± 0.1	38.0 ± 0.1	38.2 ± 0.1
Final T_{re} (C)	38.9 ± 0.1	39.3 ± 0.1	39.7 ± 0.1*

*Significantly different from control, $P < 0.05$.

group manifested initial K^+ levels that were significantly ($P < 0.01$) increased when compared to either the C or −K group. Following dehydration, K^+ levels in the −K group remained depressed when compared to either the C or +K group. Total protein concentrations were statistically significantly elevated in the +K group both pre- (vs C) and post- (vs C and −K) dehydration. Plasma osmolality (Posm) was the variable most consistently and significantly ($P < 0.01$) increased by dehydration in all groups, and was also significantly increased postdehydration when −K was compared to C.

Following dehydration, the mean plasma glucose level was elevated in the −K group compared to the C ($P < 0.01$) and the +K ($P < 0.05$) group. In the +K group predehydration, CPK was significantly ($P < 0.05$) greater than in the −K and LDH significantly ($P < 0.05$) greater than in the C groups. Both UN and creatinine were generally increased following dehydration with isolated experimental cases displaying significantly increased values when compared with controls.

Results in Table 4 demonstrate that the marked hypokalemia induced by the −K diet was also manifested in a reduced K^+ concentration and increased Na^+ level in striated muscle. Alternatively, in the kidney, liver, heart, and brain both K^+ and Na^+ concentrations remained remarkably consistent with no significant differences in either electrolyte despite the 28-day −K dietary interval. There are also indications in Table 4 (gastrocnemius, plantaris) that the level of K repletion in the +K group may not have been sufficient to maintain Na/K homeostasis in muscle despite circulatory normokalemia.

DISCUSSION

Exposure to the environmental temperature selected (31.5 C) induced significant hypohydration without marked hyperthermia or injurious sequelae (Ohara *et al.*, 1975; Horowitz *et al.*, 1983). We had earlier hypothesized (Francesconi *et al.*, 1991) that factors other than evaporative heat dissipation were responsible for the significantly increased rate of heat

Table 2. Effects of K deficiency and dehydration on plasma electrolytes, protein, and osmolality

	Control (C)		Potassium replenished (+K)		Potassium depleted (−K)	
Variable	Pre	Post	Pre	Post	Pre	Post
Na^+ (mEq l)	141.4 ± 1.1	148.5 ± 0.4***	149.6 ± 3.0*	150.2 ± 1.2	147.6 ± 2.2*	152.5 ± 0.8
K^+ (mEq l)	4.8 ± 0.1	4.5 ± 0.2	5.9 ± 0.3*	4.7 ± 0.3	3.2 ± 0.2* **	3.8 ± 0.3* **
Total protein (g/l)	6.8 ± 0.1	6.9 ± 0.1	7.3 ± 0.2*	7.6 ± 0.1*	6.9 ± 0.1	6.9 ± 0.1**
Osmolality (m Osm kg)	294.2 ± 0.9	309.4 ± 1.9***	298.0 ± 0.8	311.9 ± 1.7***	299.2 ± 1.0	316.4 ± 2.4*

*Significantly different from control, $P < 0.05$; **significantly different from +K, $P < 0.05$; ***significantly different from pre, $P < 0.05$.

Table 3. Effects of K deficiency and dehydration on several indices of heat injury

	Control (C)		Potassium replenished (+K)		Potassium depleted (−K)	
Variable	Pre	Post	Pre	Post	Pre	Post
Glucose (mg/dl)	149.4 ± 4.4	154.5 ± 3.5	147.2 ± 6.0	159.5 ± 6.8	161.9 ± 5.1	180.4 ± 7.0***
Creatine phosphokinase (U/l)	79.8 ± 14.0	76.7 ± 9.0	100.4 ± 6.0	100.8 ± 29.0	39.0 ± 4.0**	59.8 ± 16.0
Lactate dehydrogenase (U/l)	153.5 ± 20.0	101.4 ± 16.9	294.9 ± 28.0*	194.3 ± 58.0	217.4 ± 50.0	107.9 ± 17.0
Urea nitrogen (mg/dl)	16.2 ± 0.7	23.0 ± 0.8***	20.1 ± 0.9*	22.6 ± 1.6	20.6 ± 1.1*	24.2 ± 0.8***
Creatinine (mg/dl)	0.40 ± 0.01	0.44 ± 0.02	0.38 ± 0.02	0.49 ± 0.03***	0.47 ± 1.4***	0.53 ± 0.01***

*Significantly different from control, $P < 0.05$; **significantly different from +K, $P < 0.05$; ***significantly different from pre, $P < 0.05$.

gain in a K-depleted group exposed to a much higher T_{amb}. Current data seem to substantiate this hypothesis since, despite a reduced level of hypohydration and similar rates of water loss in the −K group (vs C), final T_{re} is slightly, but significantly, elevated in the −K group.

Knochel (1974) had theorized that K deficiency could compromise thermal tolerance through any of several mechanisms: altered energy transformation, loss of cell membrane integrity, inadequate endocrinological adaptations, cardiovascular insufficiency, polyuria. Hubbard *et al.* (1987) postulated that disturbances in electrolyte balance could be accompanied by increased activity of the Na/K electrogenic pump, accelerated energy utilization, and consequently elevated heat production (Saddlier and DeLuise, 1986). Thus, we (Francesconi *et al.*, 1991) speculated that elevated heating rates and reduced thermal tolerance of the K deficient rats might be attributable to increased ion pump activity and energy metabolism; in these earlier experiments the intense T_{amb} (41.5°C) and the metabolic rate overwhelmed heat dissipation of the experimental rats despite maximal evaporative heat loss (Hainsworth, 1967, 1968; Hubbard *et al.*, 1982). Currently, the moderate T_{amb} (31.5°C) provided a challenge which was compensated by the ability of both control and experimental animals to spread sufficient saliva for adequate thermoregulation. Nonetheless, both the +K and −K groups achieved final T_{re}s that were higher than that of the C group.

While increasing [Na^+] (Table 4) in muscle tissue of the +K and −K groups offsets the decrements in [K], electrolyte levels of the kidney, liver, heart, and brain were apparently unaffected by dietary treatment. This is consistent with the work of Akaike (1988) and Akaike *et al.* (1983) who concluded that the mass and [K^+] of the skeletal muscles contribute to their ability to act as buffers against K depletion in critical tissues.

Table 4. Effects of K deficiency and dehydration on electrolyte levels in muscles and organs

	Control (C)		Potassium replenished (+K)		Potassium depleted (−K)	
	Na^+	K^+	Na^+	K^+	Na^+	K^+
Tissue	(mEq/kg H_2O)		(mEq/kg H_2O)		(MEq/kg H_2O)	
Gastrocnemius	21.1 ± 1.2	125.5 ± 3.4	31.3 ± 1.9*	116.4 ± 2.8	38.0 ± 1.5***	112.4 ± 4.4*
Soleus	31.0 ± 2.8	95.1 ± 2.4	36.5 ± 2.1	94.5 ± 2.6	37.1 ± 2.4	80.4 ± 5.9***
Plantaris	21.7 ± 0.9	135.3 ± 2.4	31.9 ± 4.2*	117.7 ± 4.7*	36.3 ± 1.4*	117.4 ± 4.1*
Kidney	67.1 ± 3.3	87.8 ± 2.4	68.3 ± 4.4	84.8 ± 2.2	63.7 ± 2.8	81.0 ± 3.5
Liver	48.1 ± 3.0	114.0 ± 2.6	45.0 ± 1.9	108.2 ± 3.9	48.8 ± 1.4	112.1 ± 2.0
Diaphragm	32.0 ± 1.8	118.4 ± 2.7	32.6 ± 1.2	109.2 ± 3.2	44.3 ± 2.0***	107.7 ± 4.7
Heart	42.9 ± 1.4	104.6 ± 2.1	42.6 ± 0.8	102.1 ± 2.5	46.9 ± 1.6	100.6 ± 2.3
Brain	57.7 ± 1.4	120.6 ± 2.7	58.5 ± 1.2	114.9 ± 1.8	57.5 ± 1.3	113.8 ± 2.5

*Significantly different from control, $P < 0.05$; **significantly different from +K, $P < 0.05$.

In the tissues of interest the +K group manifested alterations in Na^+ and K^+ levels that are apparently analogous to, albeit less intense than, the rats on the −K diet. The physiological consequences and causes of these differences are not fully understood. However, it is noteworthy that the ratio of K/Na in the C diet is approx. 2.2, in the +K diet approx. 1, and, of course, there are only trace amounts of K in the −K diet. Also, factors such as differential absorption, the greatly reduced fiber in the semi-synthetic diets, and differences in the concentration of other inorganic cations may be contributing to the variability noted between the C and +K groups.

While osmolality was significantly elevated in all groups by hypohydration (Costill and Sparks, 1973), circulating Na^+ levels were significantly increased following heat exposure only in the C group; this was due to the relatively high levels of plasma Na^+, predehydration, in both the +K and −K groups. Again, the decreased K/Na in either the +K or −K diet may have contributed to the elevated circulating Na^+ in both groups, predehydration. Significant hypokalemia was achieved in the −K group, and this decrement persisted following dehydration. Other inter-group differences in indices of heat injury (e.g. protein, LDH, CPK, UN, creatinine) may not have physiological consequences since the absolute values of these means remained within normal limits.

In the current experiments preexposure glucose levels were unaffected by dietary treatment, but a significant increment in plasma glucose following heat exposure/dehydration was again (Francesconi *et al.*, 1991) observed in the K deficient rats. These results in combination with the increased final T_{re} in the −K group, also suggest an elevated heat production which may be attributable to the maintenance of electrolyte homeostasis in these animals. Alternatively, it has been confirmed (Knochel, 1984; Schaefer *et al.*, 1985) that K deficiency attenuates insulin levels and responses, and the elevated glucose levels observed in these animals following heat exposure could be related to this phenomenon.

A persistent uncertainty exists on the effects of K depletion on metabolic rate as manifested in Na/K pump activity (Na^+/K^+-adenosine triphosphatase or ouabain binding sites). For example, Clausen *et al.* (1983), Kjeldsen *et al.* (1986), and Akaike (1988) concluded that in K deficiency the loss of $[K^+]$ and elevation in $[Na^+]$ in muscle can be attributed to a reduction in Na^+/K^+-ATPase or a decrease in ouabain binding sites. Alternatively, *in vitro* studies using hamster ovary (Graves and Wheeler, 1982), chick heart (Kim *et al.*, 1984), and rat liver (Pressley *et al.*, 1986) cells have provided evidence of elevated Na^+ K^+-ATPase activity when the $[K^+]$ of the medium was reduced. The latter data support the hypothesis that tissue-specific decrements in Na^+/K^+ pump activity may be balanced or exceeded by simultaneous adaptive elevations in other tissues, but these associated responses have thus far not been confirmed.

We have concluded that moderate hypokalemia ($[K^+]$ = 3–3.5 mEq/l) did not markedly affect several physiological responses during dehydration (8–9%) elicited by passive heat exposure. However, a slightly, but significantly, elevated final T_{re} in the −K group (vs C) demonstrated that overall metabolic heat production was probably increased in this group. $[K^+]$ and $[Na^+]$ in striated muscles and critical tissues indicated that electrolyte homeostasis was maintained in kidney, liver, heart, and brain in K deficient animals. Replenishment of K^+ to the −K diet may have been inadequate to completely prevent differences between C and +K groups in tissue electrolytes despite adequate levels of circulating K in the +K group. Research is continuing on the association between electrogenic ion pump activity and heat production in K deficient rats.

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